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Patentanmeldung Nr. Patent application No. Demande de brevet n°

02251505.0

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Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

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The application was transferred from the original applicant BIOCOMPATIBLES (2) LIMITED, Farnham, Surrey, GB to the above-mentioned applicant on 09.09.02.
See for the original title of the application, page 1 of the description.

DRUG CARRIERS

The present invention relates to block copolymers for micellar delivery of drugs. It is of particular value for delivery of hydrophobic drugs.

Micelle based drug delivery systems have been developed which are based on amphiphilic copolymers. Such copolymers should have a hydrophobic moiety and a hydrophilic moiety. In a micelle, the hydrophobic moieties aggregate to form a core, with the hydrophilic moieties being revealed at the surface of the micelle where they associate with water. The micelles can solubilise poorly water-soluble drugs in their inner core. Their small size renders them suitable for systemic delivery of drugs. The core-shell structure provides some protection for the drug in the core during transport to a target cell.

Although random copolymers may be used, in which some of the monomers have hydrophobic pendant groups, most work has focussed on block copolymers. AB diblock copolymers and ABA triblock copolymers, A being the hydrophilic block and B being the hydrophobic block have been investigated. In most of the block copolymers tested to date, the hydrophilic blocks have been provided by polyethylene oxide moieties. The hydrophobic block may be a polypropylene oxide block, a hydrophobic polypeptide (such as poly(β-benzyl-L-aspartate)), a polyester (poly(DL-lactic acid)) or poly(ε-caprolactone). Polystyrene and poly(methylmethacrylate) have also been investigated as constituents of the core.

Alakhov *et al* in Biomedical Polymers and Polymer Therapeutics, 2001, eds Chiellini *et al* Kluwer Academic/Plenum publishers, New York, 121 to 137, describe the use of polyethylene oxide-polypropylene oxide block copolymers to deliver doxorubicin. Such compounds are commercially available with low poly-dispersity (of molecular weight) under the trade name Pluronic and Poloxamer (trade marks). They investigate the effect of the average molecular weight and the hydrophilic/lipophilic balance (HLB) of the block copolymer upon cytotoxicity against a panel of cell lines.

Jones *et al* in Eur. J. Pharm. Biopharm. 48(1999) 101 to 111 review the disclosures of various block copolymers as colloidal drug carriers, and explains various ways in which micelles are formed with hydrophobic drug in the core.

Inoue *et al* in J. Cont. Rel. 51 (1998) 221 to 229 describe an AB block copolymer having amphiphilic properties, in which one block is formed of methyl methacrylate (the hydrophobic core) and the other block is formed of acrylic acid units. Polymerisation is conducted by initially forming an oligomer of methylmethacrylate units, and using this as the initiator for polymerising a block of acrylic acid. The average molecular weight of the hydrophobic block was said to be 4300, although the molecular weight of the block copolymer was not stated. The physical form of the drug delivery system appeared to involve non-micellar structures, termed "unimers".

According to the present invention there is provided an aqueous composition comprising an amphiphilic block copolymer having a hydrophilic block and a hydrophobic block, dispersed in the solution, and a biologically active compound associated with the polymer, characterised in that the hydrophilic block has pendant zwitterionic groups.

The term "associated with" in the present invention means that the biologically active molecule has some association with the polymer such that its solubility, bioavailability, immunogenicity, or toxicity, is affected by the interaction with the polymer. Although the association is normally by way of the presence of micelles in which a biologically active compound is present in the core, it may involve other types of interaction, for instance the "unimer" type solutes described by Inoue *et al* (*op. cit*). It may involve covalent conjugation, but generally involves non-covalent interactions, such as electro-static, or preferably hydrophobic interactions.

Although the active may be a water-soluble drug, preferably it is relatively water-insoluble, generally soluble in an organic solvent. Generally the active has a solubility such that it has a partition coefficient (log P) between octane and water of at least 1.0, preferably at least 1.5, more

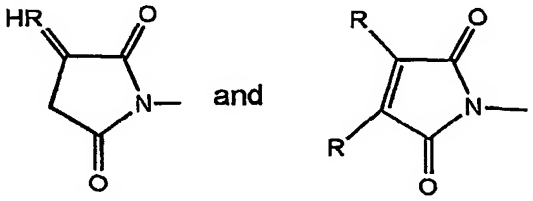
preferably at least 2.0. The active will, in the presence of micelles of the amphiphilic block copolymer used in the invention, be preferentially partitioned into the hydrophobic core of micelles, or otherwise associated with the hydrophobic block. Examples of suitable drugs are given below.

Although the hydrophilic block may be based on condensation polymers, such as polyesters, polyamides, polyanhydrides, polyurethanes, polyethers, polyimines, polypeptides, polyureas, polyacetals, polysaccharides or polysiloxanes, preferably the hydrophilic block is based on a radical polymerised addition polymer of ethylenically unsaturated monomers. Generally the monomers from which the block is formed themselves have zwitterionic pendant groups which remain unchanged in the polymerisation process. It may alternatively be possible to derivatise a functional pendant group of a monomer to render it zwitterionic after polymerisation.

Suitable ethylenically unsaturated zwitterionic monomers have the general formula

$$Y\,B\,X \qquad I$$

in which Y is an ethylenically unsaturated group selected from $H_2C{=}CR\text{-}CO\text{-}A\text{-}$, $H_2C{=}CR\text{-}C_6H_4\text{-}A^1\text{-}$, $H_2C{=}CR\text{-}CH_2A^2$, $R^2O\text{-}CO\text{-}CR{=}CR\text{-}CO\text{-}O$, $RCH{=}CH\text{-}CO\text{-}O\text{-}$, $RCH{=}C(COOR^2)CH_2\text{-}CO\text{-}O$,



A is -O- or NR^1;

A^1 is selected from a bond, $(CH_2)_lA^2$ and $(CH_2)_l\,SO_3$- in which l is 1 to 12;

A^2 is selected from a bond, -O-, O-CO-, CO-O, $CO\text{-}NR^1$-, $\text{-}NR^1\text{-}CO$, $O\text{-}CO\text{-}NR^1$-, $NR^1\text{-}CO\text{-}O$-;

R is hydrogen or $C_{1\text{-}4}$ alkyl;

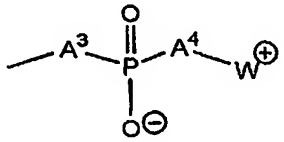
R^1 is hydrogen, C_{1-4} alkyl or BX;

R^2 is hydrogen or C_{1-4} alkyl;

B is a bond, or a straight branched alkanediyl, alkylene oxaalkylene, or alkylene (oligooxalkylene) group, optionally containing one or more fluorine substituents;

X is a zwitterionic group.

Preferably X is an ammonium, phosphonium, or sulphonium phosphate or phosphonate ester zwitterionic group, more preferably a group of the general formula II



II

in which the moieties A^3 and A^4, which are the same or different, are -O-, -S-, -NH- or a valence bond, preferably -O-, and W^+ is a group comprising an ammonium, phosphonium or sulphonium cationic group and a group linking the anionic and cationic moieties which is preferably a C_{1-12}-alkanediyl group,

preferably in which W^+ is a group of formula $-W^1-N^+R^3_3$, $-W^1-P^+R^4_3$, $-W^1-S^+R^4_2$ or $-W^1$-Het$^+$ in which:

W^1 is alkanediyl of 1 or more, preferably 2-6 carbon atoms optionally containing one or more ethylenically unsaturated double or triple bonds, disubstituted-aryl (arylene), alkylene arylene, arylene alkylene, or alkylene aryl alkylene, cycloalkanediyl, alkylene cycloalkyl, cycloalkyl alkylene or alkylene cycloalkyl alkylene, which group W^1 optionally contains one or more fluorine substituents and/or one or more functional groups; and

either the groups R^3 are the same or different and each is hydrogen or alkyl of 1 to 4 carbon atoms, preferably methyl, or aryl, such as phenyl, or two of the groups R^3 together with the nitrogen atom to which they are attached form an aliphatic heterocyclic ring containing from 5 to 7 atoms, or the three groups R^3 together with the nitrogen atom to which they are attached as heteroaromatic ring having 5 to 7 atoms, either of which rings

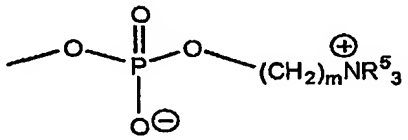
may be fused with another saturated or unsaturated ring to form a fused ring structure containing from 5 to 7 atoms in each ring, and optionally one or more of the groups R^3 is substituted by a hydrophilic functional group, and

the groups R^4 are the same or different and each is R^3 or a group OR^3, where R^3 is as defined above; or

Het is an aromatic nitrogen-, phosphorus- or sulphur-, preferably nitrogen-, containing ring, for example pyridine.

Monomers in which X is of the general formula in which W^+ is $W^1N^{\oplus}R^3_3$ may be made as described in our earlier specification WO-A-9301221. Phosphonium and sulphonium analogues are described in WO-A-9520407 and WO-A-9416749.

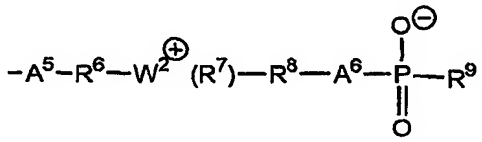
Generally a group of the formula II has the preferred general formula III



III

where the groups R^5 are the same or different and each is hydrogen or C_{1-4} alkyl, and m is from 1 to 4, in which preferably the groups R^5 are the same preferably methyl.

In phosphobetaine based groups, X may have the general formula IV



IV

in which A^5 is a valence bond, -O-, -S- or -NH-, preferably -O-;

R^6 is a valence bond (together with A^5) or alkanediyl, -C(O)alkylene- or -C(O)NH alkylene preferably alkanediyl, and preferably containing from 1 to 6 carbon atoms in the alkanediyl chain;

W^2 is S, PR^7 or NR^7;

the or each group R^7 is hydrogen or alkyl of 1 to 4 carbon atoms or the two groups R^7 together with the heteroatom to which they are attached form a heterocyclic ring of 5 to 7 atoms;

R^8 is alkanediyl of 1 to 20, preferably 1 to 10, more preferably 1 to 6 carbon atoms;

A^6 is a bond, NH, S or O, preferably O; and

R^9 is a hydroxyl, C_{1-12} alkyl, C_{1-12} alkoxy, C_{7-18} aralkyl, C_{7-18} -aralkoxy, C_{6-18} aryl or C_{6-18} aryloxy group.

Monomers comprising a group of the general formula IV may be made by methods as described in JP-B-03-031718, in which an amino substituted monomer is reacted with a phospholane.

In compounds comprising a group of the general formula IV, it is preferred that

A^5 is a bond;

R^6 is a C_{2-6} alkanediyl;

W^2 is NR^7:

each R^7 is C_{1-4} alkyl;

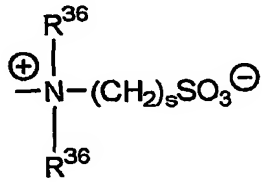
R^8 is C_{2-6} alkanediyl;

A^6 is O; and

R^9 is C_{1-4} alkoxy.

Alternatively X may be a zwitterion in which the anion comprises a sulphate, sulphonate or carboxylate group.

One example of such a group is a sulphobetaine group, of the general formula XI



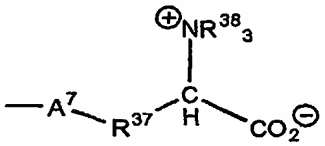
XI

where the groups R^{36} are the same or different and each is hydrogen or C_{1-4} alkyl and s is from 2 to 4.

Preferably the groups R^{36} are the same. It is also preferable that at least one of the groups R^{36} is methyl, and more preferable that the groups R^{36} are both methyl.

Preferably s is 2 or 3, more preferably 3.

Another example of a zwitterionic group having a carboxylate group is an amino acid moiety in which the alpha carbon atom (to which an amine group and the carboxylic acid group are attached) is joined through a linker group to the backbone of the biocompatible polymer. Such groups may be represented by the general formula XII



XII

in which A^7 is a valence bond, -O-, -S- or -NH-, preferably -O-,

R^{37} is a valence bond (optionally together with A^7) or alkanediyl, -C(O)alkylene- or -C(O)NHalkylene, preferably alkanediyl and preferably containing from 1 to 6 carbon atoms; and

the groups R^{38} are the same or different and each is hydrogen or alkyl of 1 to 4 carbon atoms, preferably methyl, or two or three of the groups R^{38}, together with the nitrogen to which they are attached, form a heterocyclic ring of from 5 to 7 atoms, or the three group R^{38} together with the nitrogen atom to which they are attached form a fused ring heterocyclic structure containing from 5 to 7 atoms in each ring.

Another example of a zwitterion having a carboxylate group is a carboxy betaine $-N^{\oplus}(R^{39})_2(CH_2)_rCOO^{\ominus}$ in which the R^{39} groups are the same or different and each is hydrogen or R_{1-4} alkyl and r is 2 to 6, preferably 2 or 3.

In the zwitterionic monomer of the general formula I it is preferred that the ethylenic unsaturated group Y is $H_2C=CR-CO-A-$. Such acrylic moieties are preferably methacrylic, that is in which R is methyl, or acrylic, in which R is hydrogen. Whilst the compounds may be (meth)acrylamido compounds

(in which A is NR^1), in which case R^1 is preferably hydrogen, or less preferably, methyl, most preferably the compounds are esters, that is in which A is O.

In monomers of the general formula I, especially where Y is the preferred (alk)acrylic group, B is most preferably an alkanediyl group. Whilst some of the hydrogen atoms of such group may be substituted by fluorine atoms, preferably B is an unsubstituted alkanediyl group, most preferably a straight chain group having 2 to 6 carbon atoms.

A particularly preferred zwitterionic monomer is 2-methacryloyloxyethyl-2'-trimethylammonium ethyl phosphate inner salt.

The hydrophobic block may be formed of condensation polymers, such as polyethers, polyesters, polyamides, polyanhydrides polyurethanes, polyethers, polyimines, polypeptides, polyureas, polyacetals, polysaccharides or polysiloxanes. One example of a suitable hydrophobic block is polyalkylene oxide, usually polypropylene oxide, that is the same type of block as has been used in the well-studied Pluronic/Poloxamer based systems. Another is polyethyleneimine, copolymers of which with polyalkylene oxides have been investigated as drug delivery components. Generally the type of polymer forming the hydrophobic block is the same as that forming the hydrophilic block. Preferably the polymer is formed by radical polymerisation of ethylenically unsaturated monomers.

The hydrophobic block may be nonionic and substantially non-ionisable under pH conditions in the range 4 to 10. Preferably, however, the hydrophobic block comprises pendant groups which are ionisable, having a pK_A or pK_B in the range 4 to 10, preferably in the range 5 to 9, for instance in the range 6 to 8. In the specification, the pK_A or pK_B, as the case may be, of a group in a polymer is determined on the basis of a polymer system (and not assumed to be the same as the pK_A's or pK_B's of similar moieties in non-polymeric systems).

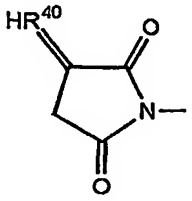
It is preferred that the hydrophobic block comprise pendant cationisable moieties preferably as pendant groups. Cationisable moieties

are, for instance, primary, secondary or tertiary amines, capable of being protonated at pH's in the range 4 to 10. Alternatively the group may be a phosphine.

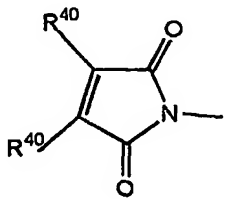
Suitable monomers from which the hydrophobic block is formed have the general formula

$$Y^1B^1Q$$

in which Y^1 is selected from $H_2C=CR^{40}-CO-A^8-$, $H_2C=CR^{40}-C_6H_4-A^9-$, $H_2C=CR^{40}-CH_2A^{10}$, $R^{42}O-CO-CR^{40}=CR^{40}-CO-O$, $R^{40}CH=CH-CO-O-$, $R^{40}CH=C(COOR^2)CH_2-CO-O$,



and



A^8 is -O- or NR^{41};

A^9 is selected from a bond, $(CH_2)_qA^{10}$ and $(CH_2)_q\ SO_3$- in which q is 1 to 12;

A^{10} is selected from a bond, -O-, O-CO-, CO-O-, $CO-NR^{41}$-, $-NR^{41}-CO-$, $O-CO-NR^{41}-$, $NR^{41}-CO-O-$;

R^{40} is hydrogen or C_{1-4} alkyl;

R^{41} is hydrogen, C_{1-4} alkyl or B^1Q;

R^{42} is hydrogen or C_{1-4} alkyl;

B^1 is a bond, or a straight branched alkanediyl, alkylene oxaalkylene, or alkylene (oligooxalkylene) group, optionally containing one or more fluorine substituents; and

Q is a cationic or cationisable group of the formula $-NR^{43}_p$, $-PR^{43}_p$ and SR^{43}_r, in which p is 2 or 3, r is 1 or 2, the groups R^{43} are the same or different and each is selected from the group consisting of hydrogen, C_{1-24} alkyl and aryl, or two of the groups R^{43} together with the heteroatom to which they are attached from a 5 to 7 membered heterocyclic ring or three R^{43} groups together with the heteroatom to which they are attached form a 5 to 7

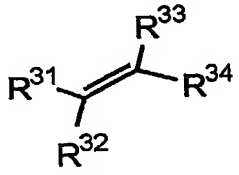
membered heteroaromatic ring, either of which rings may be fused to another 5 to 7 membered saturated or unsaturated ring, and any of the R^{43} groups may be substituted by amino or hydroxyl groups or halogen atoms.

Preferably Y^1 is $H_2C=CR^{40}$-CO-A^8- where R^{40} is H or methyl and A^8 is O or NH.

Preferably Q is NR^{43}_2 where R^{43} is C_{1-12}-alkyl. Preferably both R^{43}'s are the same. Particularly useful results have been achieved where the groups R^{43} are C_{1-4} alkyl, especially ethyl.

Either or both the hydrophobic and hydrophilic blocks may include comonomers, for instance to provide functionality, control over hydrophobicity, control over pH sensitivity, pK_A or pK_B as the case may be, or as general diluents. For instance comonomers providing functionality may be useful to provide conjugation of pendant groups following polymerisation and/or micelle formation, to targeting moieties, or to provide for conjugation between the biologically active molecule and the polymer. Alternatively, functional groups may allow for crosslinking of the polymer following micelle formation, to confer increased stability on the micellar structure.

Examples of suitable comonomers are compounds of the general formula X



X

in which R^{31} is selected from hydrogen, halogen, C_{1-4} alkyl and groups $COOR^2$ in which R^2 is hydrogen and C_{1-4} alkyl;

R^{32} is selected from hydrogen, halogen and C_{1-4} alkyl;

R^{33} is selected from hydrogen, halogen, C_{1-4} alkyl and groups $COOR^2$ provided that R^{31} and R^{33} are not both $COOR^2$; and

R^{34} is a C_{1-10} alkyl, a C_{1-20} alkoxycarbonyl, a mono-or di-(C_{1-20} alkyl) amino carbonyl, a C_{6-20} aryl (including alkaryl) a C_{7-20} aralkyl, a C_{6-20}

aryloxycarbonyl, a C_{1-20} -aralkyloxycarbonyl, a C_{6-20} arylamino carbonyl, a C_{7-20} aralkyl-amino, a hydroxyl or a C_{2-10} acyloxy group, any of which may have one or more substituents selected from halogen atoms, alkoxy, oligo-alkoxy, aryloxy, acyloxy, acylamino, amine (including mono and di-alkyl amino and trialkylammonium in which the alkyl groups may be substituted), carboxyl, sulphonyl, phosphoryl, phosphino, (including mono- and di- alkyl phosphine and tri-alkylphosphonium), zwitterionic, hydroxyl groups, vinyloxycarbonyl and other vinylic or allylic substituents, and reactive silyl or silyloxy groups, such as trialkoxysilyl groups;

or R^{34} and R^{33} or R^{34} and R^{32} may together form -$CONR^{35}CO$ in which R^{35} is a C_{1-20} alkyl group.

It is preferred for at least two of the groups $R^{31}R^{32,}R^{33}$ and R^{34} to be halogen or, more preferably, hydrogen atoms. Preferably R^{31} and R^{32} are both hydrogen atoms. It is particularly preferred that compound of general formula X be a styrene-based or acrylic based compound. In styrene based compounds R^{34} represents an aryl group, especially a substituted aryl group in which the substituent is an amino alkyl group, a carboxylate or a sulphonate group. Where the comonomer is an acrylic type compound, R^{34} is an alkoxycarbonyl, an alkyl amino carbonyl, or an aryloxy carbonyl group. Most preferably in such compounds R^{34} is a C_{1-20} -alkoxy carbonyl group, optionally having a hydroxy substituent. Acrylic compounds are generally methacrylic in which case R^{33} is methyl.

Preferably the comonomer is a non-ionic comonomer, such as a C_{1-24} alkyl(alk)-acrylate or -acrylamide, mono- or di- hydroxy-C_{1-6}-alkyl(alk)-acrylate, or acrylamide, oligo(C_{2-3} alkoxy) C_{2-18}-alkyl (alk)-acrylate, or -acrylamide, styrene, vinylacetate or N-vinyllactam.

The block copolymer may be a simple A-B block copolymer, or may be an A-B-A or B-A-B block copolymer (where A is the hydrophilic block and B is the hydrophobic block). It may also be an A-B-C, A-C-B or B-A-C block copolymer, where C is a different type of block. C blocks may, for instance, comprise functional, e.g. cross-linking or ionic groups, to allow for reactions

of the copolymer, for instance in the novel compositions. Crosslinking reactions especially of A-C-B type copolymers, may confer useful stability on drug-containing micelles. Cross-linking may be covalent, or sometimes, electrostatic in nature. Cross-linking may involve addition of a separate reagent to link functional groups, such as using a difunctional alkylating agent to link two amino groups.

For optimum micelle formation, the block copolymers should have controlled molecular weights. It is preferable for each of the blocks to have molecular weight controlled within a narrow band, that is to have a narrow polydispersity. The polydispersity of molecular weight should, for instance, be less than 2.0, more preferably less than 1.5, for instance in the range 1.1 to 1.4.

The degree of polymerisation of the hydrophobic block is in the range 5 to 2000, preferably 10 to 500, more preferably 10 to 250. The hydrophilic block has a degree of polymerisation in the range 2 to 1000, preferably 5 to 250 more preferably 10 to 100. Generally the relative lengths of the hydrophobic to hydrophilic blocks is in the range 1:5 to 10:1, preferably 1:1 to 5:1.

It may be possible to synthesise the block copolymer by initial formation of a low poly dispersity, low molecular weight initial block using control of initiator and chain transfer agent (which permanently terminates chain formation), with the initial block then being derivatised to act as a suitable radical initiator in a subsequent block forming step, by the technique described by Inoue *et al op. cit.*. Preferably, however, the polymerisation of at least one of the blocks is by controlled radical polymerisation for instance a living radical polymerisation process.

A living radical polymerisation process may be a group transfer radical polymerisation, for instance in which an N→O, or other carbon-, sulphur-, and oxygen- centered radical group is transferred from an initiator compound to a monomer. Preferably, however, the process is an atom

transfer radical polymerisation process. Preferably such a process is used to form each block of the block copolymer.

In the atom or group transfer radical polymerisation process, the initiator has a radically transferable atom or group, and the catalyst comprises a transition metal compound and a ligand, in which the transition metal compound is capable of participating in a redox cycle with the initiator and dormant polymer chain, and the ligand is either any N-, O-, P- or S-containing compound which can coordinate with the transition metal atom in a σ-bond, or any carbon-containing compound which can coordinate with the transition metal in a π-bond, such that direct bonds between the transition metal and growing polymer radicals and not formed.

Preferably the radical initiator is of the general formula V

$$R^{11}R^{12}R^{13}C\text{-}X^2 \qquad V$$

where:

X^2 is selected from the group consisting of Cl, Br, I, OR^{10}, SR^{14}, SeR^{14}, $OP(=O)R^{14}$, $OP(=O)(OR^{14})_2$, $O\text{-}N(R^{14})_2$ and $S\text{-}C(=S)N(R^{14})_2$, where R^{10} is alkyl of from 1 to 20 carbon atoms in which each of the hydrogen atoms may be independently replaced by halide, R^{14} is aryl or a straight or branched C_1-C_{20} alkyl group, and where an $N(R^{14})_2$ group is present, the two R^{14} groups may be joined to form a 5- or 6-membered heterocyclic ring; and

R^{11}, R^{12} and R^{13} are each independently selected from the group consisting of H, halogen, C_1-C_{20} alkyl, C_3-C_8 cycloalkyl, $C(=O)R^{15}$, $C(=O)NR^{16}R^{17}$, COCl, OH, CN, C_2-C_{20} alkenyl, C_2-C_{20} alkenyl oxiranyl, glycidyl, aryl, heterocyclyl, aralkyl, aralkenyl, C_1-C_6 alkyl in which from 1 to all of the hydrogen atoms are replaced with halogen, C_1-C_6 alkyl substituted with from 1 to 3 substituents selected from the group consisting of C_1-C_4 alkoxy, aryl, heterocyclyl, $C(=O)R^{15}$, $C(=O)NR^{16}R^{17}$, $-CR^{12}R^{13}X^2$, oxiranyl and glycidyl;

where R^{15} is alkyl of from 1 to 20 carbon atoms, alkoxy of from 1 to 20 carbon atoms, oligo(alkoxy) in which each alkoxy group has 1 to 3 carbon

atoms, aryloxy or heterocyclyloxy any of which groups may have substituents selected from optionally substituted alkoxy, oligoalkoxy, amino (including mono- and di-alkyl amino and trialkyl ammonium, which alkyl groups, in turn may have substituents selected from acyl, alkoxycarbonyl, alkenoxycarbonyl, aryl and hydroxy) and hydroxyl groups; and

R^{16} and R^{17} are independently H or alkyl of from 1 to 20 carbon atoms which alkyl groups, in turn may have substituents selected from acyl, alkoxycarbonyl, alkenoxycarbonyl, aryl and hydroxy, or R^{16} and R^{17} may be joined together to form an alkanediyl group of from 2 to 5 carbon atoms, thus forming a 3- to 6-membered ring;

such that not more than two of R^{11}, R^{12} and R^{13} are H.

In the initiator of the general formula V it is preferred that no more than one of R^{11}, R^{12} and R^{13}, and preferably none, is hydrogen. Suitably at least one, and preferably both of R^{11} and R^{12} is methyl. R^{13} is suitably a group CO-R^{15} in which R^{15} is preferably alkoxy of from 1 to 20 carbon atoms, oligo(alkoxy) in which each alkoxy group has 1 to 3 carbon atoms, aryloxy or heterocyclyloxy any of which groups may have substituents selected from optionally substituted alkoxy, oligoalkoxy, amino (including mono-- and di-alkyl amino and trialkyl ammonium, which alkyl groups, in turn may have substituents selected from acyl, alkoxycarbonyl, alkenoxycarbonyl, aryl and hydroxy) and hydroxyl groups.

Since any of R^{11}, R^{12} and R^{13} may comprise a substituent $C^{12}R^{13}X^2$, the initiator may be di-, oligo- or poly- functional.

Selection of a suitable initiator is based on various considerations. Where the polymerisation is carried out in the liquid phase, in which the monomers are dissolved, it is preferable for the initiator to be soluble in that liquid phase. The initiator is thus selected for its solubility characteristics according to the solvent system which in turn is selected according to the monomers being polymerised.

Water-soluble initiators include, for instance the reaction product of monomethoxy-capped oligo(ethylene oxide) with 2-bromoisobutyryl bromide

(OEGBr), 4-bromo-α-toluic acid or ethyl 2-bromopropanoic acid or 2-(N,N-dimethylamino) ethyl-2'-bromoisobutyrate.

The portion of the initiator -C-$R^{11}R^{12}R^{13}$ becomes joined to the first monomer of the growing polymer chain. The group X^2 becomes joined to the terminal unit of the polymer chain. Selection of a suitable initiator is determined in part by whether a terminal group having particular characteristics is required for subsequent functionality. Subsequent reactions of the product polymer are described below. The residue of the initiator at one or other end of the polymer may be reacted with biologically active moieties, such as targetting groups. Alternatively the initiator itself may comprise a group conferring useful targetting or other biological activity in the product polymer.

In an atom or group radical transfer polymerisation process the transition metal compound which comprises a component of the catalyst is $M_t^{n+}X'_n$, where:

M_t^{n+} may be selected from the group consisting of Cu^{1+}, Cu^{2+}, Fe^{2+}, Fe^{3+}, Ru^{2+}, Ru^{3+},Cr^{2+}, Cr^{3+}, Mo^{2+}, Mo^{3+}, W^{2+}, W^{3+}, Mn^{2+}, Mn^{3+}, Mn^{4+}, Rh^{3+}, Rh^{4+}, Re^{2+}, Re^{3+}, Co^{+}, Co^{2+}, Co^{3+}, V^{2+}, V^{3+}, Zn^{+}, Zn^{2+}, Ni^{2+}, Ni^{3+}, Au^{+}, Au^{2+}, Ag^{+} and Ag^{2+};

X' is selected from the group consisting of halogen, C_1-C_6-alkoxy, $(SO_4)_{½}$, $(PO_4)_{1/3}$, $(R^{18}PO_4)½$, $(R^{18}{}_2PO_4)$, triflate, hexafluorophosphate, methanesulphonate, arylsulphonate, CN and $R^{19}CO_2$, where R^{18} is aryl or a straight or branched C_{1-20} alkyl and R^{19} is H or a straight or branched C_1-C_6 alkyl group which may be substituted from 1 to 5 times with a halogen; and

n is the formal charge on the metal ($0 \leq n \leq 7$).

Preferably X' is halide, most preferably chloride or bromide. Particularly suitable transition metal compounds are based on copper or ruthenium, for instance CuCl or $RuCl_2$.

In the catalyst, the ligand is preferably selected from the group consisting of:

a) compounds of the formulas:

R^{20}-Z-R^{21} and

R^{20}-Z-$(R^{22}$-Z$)_m$-R^{21}

where:

R^{20} and R^{21} are independently selected from the group consisting of H, C_1-C_{20} alkyl, aryl, heterocyclyl and C_1-C_6 alkoxy, C_1-C_4 dialkylamino, C(=O)R^{22}, C(=O)$R^{23}R^{24}$ and A^7C(=O)R^{25}, where A^7 may be NR^{26} or O; R^{22} is alkyl of from 1 to 20 carbon atoms, aryloxy or heterocyclyloxy; R^{23} and R^{24} are independently H or alkyl of from 1 to 20 carbon atoms or R^{23} and R^{24} may be joined together to form an alkanediyl group of from 2 to 5 carbon atoms, thus forming a 3- to 6-membered ring; R^{25} is H, straight or branched C_1-C_{20} alkyl or aryl and R^{26} is hydrogen, straight or branched; C_{1-20}-alkyl or aryl; or R^{20} and R^{21} may be joined to form, together with Z, a saturated or unsaturated ring;

Z is O, S, NR^{27} or PR^{27}, where R^{27} is selected from the same group as R^{20} and R^{21}, and where Z is PR^{27}, R^{27} can also C_1-C_{20} alkoxy or Z may be a bond, CH_2 or a fused ring, where one or both of R^{20} and R^{21} is heterocyclyl,

each R^{22} is independently a divalent group selected from the group consisting of C_1-C_8 cycloalkanediyl, C_1-C_8 cycloalkenediyl, arenediyl and heterocyclylene where the covalent bonds to each Z are at vicinal positions or R^{22} may be joined to one or both of R^{20} and R^{21} to formulate a heterocyclic ring system; and

m is from 1 to 6;

b) CO;

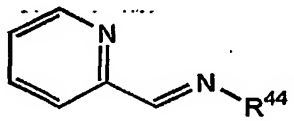
c) porphyrins and porphycenes, which may be substituted with from 1 to 6 halogen atoms, C_1-$_6$ alkyl groups, C_{1-6}-alkoxy groups, C_{1-6} alkoxycarbonyl, aryl groups, heterocyclyl groups, and C_{1-6} alkyl groups further substituted with from 1 to 3 halogens;

d) compounds of the formula $R^{23}R^{24}$C(C(=O)R^{25})$_2$, where R^{25} is C_{1-20} alkyl, C_{1-20} alkoxy, aryloxy or heterocyclyloxy; and each of R^{23} and R^{24} is

independently selected from the group consisting of H, halogen, C_{1-20} alkyl, aryl and heterocyclyl, and R^{23} and R^{24} may be joined to form a C_{1-8} cycloalkyl ring or a hydrogenated aromatic or heterocyclic ring, of which the ring atoms may be further substituted with 1 to 5 C_{1-6} alkyl groups, C_{1-6} alkoxy groups, halogen atoms, aryl groups, or combinations thereof; and

e) arenes and cyclopentadienyl ligands, where said cyclopentadienyl ligand may be substituted with from one to five methyl groups, or may be linked through and ethylene or propylene chain to a second cyclopentadienyl ligand.

Selection of a suitable ligand is, for instance, based upon the solubility characteristics and/or the separability of the catalyst from the product polymer mixture. Generally it is catalyst to be soluble in a liquid reaction mixture, although under some circumstances it may be possible to immobilise the catalyst, for instance an a porous substrate. For the preferred process, which is carried out in the liquid phase, the ligand is soluble in a liquid phase. The ligand is generally a nitrogen containing ligand. The preferred ligand may be a compound including a pyridyl group and an imino moiety, such as bipyridine, or



where R^{44} is a suitable alkyl group, the substituent being variable and adaptable to confer desired solubility characteristics or may be triphenylphosphine or 1,1,4,7,10,10-hexamethyl-triethylene tetramine.

Such ligands are usefully used in combination with copper chloride and ruthenium chloride transition metal compounds as part of the catalyst.

A living radical polymerisation process is preferably carried out to achieve a degree of polymerisation in the or each block in the range 2 to 2000. Preferably the degree of polymerisation is in the range 5 to 1000, more preferably in the range 10 to 100. In the preferred group or atom

transfer radical polymerisation technique, the degree of polymerisation is directly related to the initial ratios of initiator to monomer. Preferably the ratio is in the range 1:(2 to 2000), more preferably in the range of 1:(5 to 1000), most preferably in the range 1:(10 to 100).

The ratio of metal compound and ligand in the catalyst should be approximately stoichiometric, based on the ratios of the components when the metal ion is fully complexed. The ratio should preferably be in the range 1:(0.5 to 2) more preferably in the range 1:(0.8:1.25). Preferably the range is about 1:1.

In the living radical polymerisation process, the catalyst may be used in amounts such that a molar equivalent quantity as compared to the level of initiator is present. However, since catalyst is not consumed in the reaction, it is generally not essential to include levels of catalyst as high as of initiator. The ratio of catalyst (based on transition metal compound) to initiator is preferably in the range 1:(1 to 50), more preferably in the range 1:(1 to 10).

Whilst the polymerisation reaction may be carried out in the gaseous phase, it is more preferably carried out in the liquid phase. The reaction may be heterogeneous, that is comprising a solid and a liquid phase, but is more preferably homogeneous. Preferably the polymerisation is carried out in a single liquid phase. Where the monomer is liquid, it is sometimes unnecessary to include a non-polymerisable solvent. More often, however, the polymerisation takes place in the presence of a non-polymerisable solvent. The solvent should be selected having regard to the nature of the zwitterionic monomer and any comonomer, for instance for its suitability for providing a common solution containing both monomers. The solvent may comprise a single compound or a mixture of compounds.

It has been found that, especially where the zwitterionic monomer is MPC, that it is desirable to include water in the polymerisation mixture. Preferably water should be present in an amount in the range 10 to 100% by weight based on the weight of ethylenically unsaturated monomer. Preferably the total non-polymerisable solvent comprised 1 to 500% by

weight based on the weight of ethylenically unsaturated monomer. It has been found that the zwitterionic monomer and water should be in contact with each other for as short a period as possible prior to contact with the initiator and catalyst. It may be desirable therefore for all the components of the polymerisation other than the zwitterionic monomer to be premixed and for the zwitterionic monomer to be added to the premix as the last additive.

It is often desired to copolymerise MPC or other zwitterionic monomer with a comonomer which is insoluble in water. In such circumstances, a solvent or co-solvent (in conjunction with water) is included to confer solubility on both MPC and the more hydrophobic monomer. Suitable organic solvents are ethers, esters and, most preferably, alcohols. Especially where a mixture of organic solvent and water is to used, suitable alcohols are C_{1-4} -alkanols. Methanol is found to be particularly suitable in the polymerisation process of the invention.

The process may be carried out at raised temperature, for instance up to 60 to 80 °C. However it has been found that the process proceeds sufficiently fast at ambient temperature.

The living radical polymerisation process has been found to provide polymers of zwitterionic monomers having a polydispersity (of molecular weight) of less than 1.5, as judged by gel permeation chromatography. Polydispersities in the range 1.2 to 1.4 for the or each block are preferred.

According to a further aspect of the invention there is provided a new method of forming an aqueous composition comprising an amphiphilic block copolymer and a biologically active compound, in which the copolymer comprises a hydrophilic block and a hydrophobic block and an aqueous dispersion of empty copolymer micelles is formed and the micellar dispersion is contacted with biologically active compound under conditions such that the biologically active compound becomes associated with the copolymer in the micelles, characterised in that the hydrophilic block has pendant zwitterionic groups.

Where the composition of the invention comprises micelles of block copolymer with biologically active molecule in the core, this may be formed by a variety of techniques. The process may involve simple equilibration of the drug and polymer micelles in water, at a concentration above the critical micelle concentration (CMC) of the block copolymer. For instance drug may be contacted in solid form with an aqueous dispersion of polymer micelles and incubated, optionally with shaking, to solubilise the active in the dispersed micelles. Alternatively, drug dissolved in organic solvent may be emulsified into an aqueous dispersion of polymer micelles, whereby solvent and biologically active compound become incorporated into the core of the micelles, followed by evaporation of solvent from the system.

An advantage of the present invention where the hydrophobic block is pH sensitive, is that micelles may be loaded using a pH change system. In such a process, polymer is dispersed in aqueous liquid in ionised form, in which it solubilises at relatively high concentrations without forming micelles. Subsequently the pH is changed such that some or all of the ionised groups become deprotonated so that they are in non-ionic form. At the second pH, the hydrophobicity of the block increases and micelles are formed spontaneously. Micelles may be loaded by contacting the empty micellar composition with biologically active, either in solid form or in dissolved form in an organic solvent. Solvent may optionally be removed in a subsequent step, e.g. by evaporation. It is found that loading of a model hydrophobic drug from a film on the inner surface of a vessel containing the empty polymer micelles generated micellised drug after reasonable periods.

There follows a list of drugs for which the present invention may be useful with values for the log P, calculated using the log Pcalculator at daylight.com and as determined experimentally, where the information is available, are listed below. Drugs having log P (i.e. determined experimentally) or clog P (i.e. recalculated) greater than 1.0, preferably greater than 1.5 or 2.0 are particularly suitable.

Drug	Log P (calc)	Mw	LogP (Exp)	Reference
Actinomycin		1255.44	0.997	
Angiopeptin	3.61	1009.23		
Aspirin		180.16	1.23	*Hansch J Org Chem 32/2583/1967*
Atorvastatin		558	1.61	
Batimastat	2.446	477		
Carmofur			2.63	
Carmustine				
Carvedilol	4.041	406		
Cerivastatin		459	2.05	
Cilostazol		369	2.3	
Dexamethasone		392.5	1.83	*Hansch et al 1995*
Dipyramidole	2.532	504.63		
Doxorubicin	1.04	580		
Estradiol		272.39	4.3	*Acta Pharm Suec 16/151/1979*
Etoposide		588.6	0.99	*Pharmaceutical Research 6/5/408/1989*
Fluorodeoxyuridine			-1.16	
Fluorouracil		130	-1	
Fluvastatin		411	1.67	
Gemcitabine	0.834	263		
Irinotecan	2.521	622		
Leflunomide	2.2227	270		
L-Leucovirin	-3.2			
Lomustine	2.14			
Lovastatin		404	1.7	
Marimastat	0.756	331		
Methylprednisolone	1.42	374.5		
Methotrexate		454	-1.8	*Pharmaceutical research 7/7/712/1990*
Mitomycin C	-3.221			
Mitoxantrone	0.239			
Orange OT	4.01	262		
Pravastatin		424	-0.23	
Prinomastat	2.93	411		
Rapamycin	7.76	914.2		
Roxithromycin	2.04	837.06		
Simvastatin		418	2.06	
Taxol		853.9	3.98	*J. Pharm Sci 85/2/228/1996*
Taxotere	5.86			
6-Thioguanine		167	-0.28	
Tirofiban	0.46	440.6		
Topotecan	1.757	421		
Tranilast	-1.09	327.3		
Vinblastine		814	1.68	*Cancer Chemother Pharmacol 26/4/263/1990*
Vincristine Sulfate		923	2.14	*Cancer Chemother Pharmacol 26/4/263/1990*

Micellised drug delivery systems have been used for cytotoxic drugs,

for instance used in anti-cancer and/or anti-angiogenic therapies, and such drugs may be used in the present invention. Examples are doxorubicin, daunomycin and paclitaxel and analogues and derivatives thereof.

The following figures illustrate the invention:

Figure 1 indicates the results of example 1.

Figure 2 illustrates the effective pH on the solubilisation of a hydrophobic drug for block copolymers used in the invention.

Figure 3 shows the particle size distribution of micelles formed in the examples.

The invention is illustrated in the accompanying examples.

Example 1

A-B block copolymers were formed by an atom transfer polymerisation with MPC being homopolymerised in a first block forming step using an oligo(ethylene glycol) initiator as described by Ashford E.J. *et al* in Chem. Commun. 1999, 1285 (the reaction product of monomethoxy-capped oligo(ethylene glycol) and 2-bromoisobutyryl bromido) in the presence of bipyridine ligand and copper (I) bromide catalyst DEA (diethylaminoethyl methacrylate) was polymerised in a second block forming step. The degree of polymerisation for each block is indicated in Table 1 showing the results.

The reaction conditions were [MPC] = 2.02M (6.0g in 10ml methanol), [MPC]: [OEG-Br]:[CuBr]:[bipy] = (30 or 20 as shown in Table 1):1:1:2, T = 20°C; MPC was polymerised first in all cases followed by addition and polymerisation of an appropriate amount of neat DEA. Almost complete monomer conversion was achieved after the time indicated in Table 1 for the diblock, as indicated by ^{1}H NMR spectroscopy (no residual vinyl double bonds). The reaction mixture was diluted with methanol and passed through a silica column to remove residual ATRP catalyst. After solvent evaporation, the products were dried under vacuum at room temperature.

Table 1: Data of the polymerization of MPC – DEAEMA diblock copolymers in methanol

Ex #	Comonomer	MPC in copolymer (mol %)	TargetDp	[Amine] (M)	Time for > 99% Conversion		Mn (AGPC)		Mw / Mn	
					MPC HOMO (mins)	MPC Diblock (h)	MPC(a) HOMO	MPC(b) Diblock	MPC HOMO	MPC Diblock
1	DEA	50	20:20	1.35	180	20	6200	14000	1.15	1.22
2	DEA	33	10:20	1.35	180	21	3500	11000	1.17	1.29
3	DEA	50	30:30	2.02	130	20	10000	21000	1.18	1.30
4	DEA	33	30:60	4.04	130	22	11000	31000	1.19	1.29
5	DEA	23	30:100	6.73	130	23	11000	43000	1.19	1.28

DEA = diethylaminoethylmethacrylate

AGPC = aqueous gel permeation chromatography

The MPC-DEA block copolymers were dissolved in McIlvaines buffer at a concentration of 1mM and at pH 4. The pH was then adjusted upwards with NaOH to pH 8, and 10.8, so the micelles would form. A series of half dilutions were then prepared from the micellised polymers, using McIlvaines buffer of the same pH as the polymer solution. The hydrophobic dye Orange OT (Sigma-Aldrich) (which has a log P of about 4) (supplied as 0.1% w/v in ethanol) had been previously coated into the wells of a 96 well assay plate (Bibby Sterilin). The dilutions of the micellised polymer solutions were then applied to individual coated wells of the assay plate, and incubated for 18 hours at 37°C. The samples were then transferred to fresh uncoated 96 well plates, and the absorbance measured at 492nm using a Microtek 96 well plate reader. The readings obtained were converted to percentage solubilisation of Orange OT, as an indication of drug loading potential. To demonstrate the polymer shift from unimer to micelle state in response to pH increase, a control of polymer at pH 4 was carried using the same technique and conditions as that used for the pH8 and pH10.8 samples. The polymer solutions at pH4 and pH8 were also analysed using photon correlation spectroscopy (PCS) to measure the hydrodynamic diameter of the particles based on the intensity of scattered light, and calculated using the Stokes-Einstein equation, as described in ISO13321 British Standards Institution. 1997, BS3046: Part 8: 1997: ISO 13321: "Photon correlation spectroscopy", in Methods for determination of particle size distribution, BSI publications, Chiswick, UK, p 1-21, with subsequent analysis and determination of intensity size distributions using the CONTIN algorithm. Measurement was carried out using a Malvern Zetasizer 3000HS, using a 10mW He-Ne laser, with a wavelength of 633nm, and a high sensitivity avalanche photodiode detector fixed at a 90 degree angle to the laser, at a temperature of 25°C. Samples were sonicated for 5 minutes and filtered through a 0.2 micron filter prior to measurement, to remove any aggregation and possible dust contamination.

Results and Discussion

The results of the assays can be seen in Figures 1,2 and 3. It can be seen from the results in Figure 1 that the MPC-DEMA micelle systems are capable of entrapping the hydrophobic drug analogue, in the form of the Orange OT dye. As pH was raised, from pH 8 to pH 10.8, the amount of Orange OT solubilised increased, and as the DEA block length and DEA to MPC ratio increased the Orange OT solubilisation again increased. The increased pH would have resulted in an increased hydrophobicity of the DEA blocks and given a greater level of micelle completion. The increased DEA block length would have produced a larger central micelle core, resulting in an increase in entrapment of hydrophobic dye.

In Figure 2 it can be seen that at pH4 the polymer solution (using the 30:60 MPC:DEA copolymer) does not display the same increase in absorbance as that of the pH8 solution. This suggest that micelles as not present at pH4, and thus the hydrophobic dye is not solubilised, whilst at pH8 micelles are present and the Orange OT dye is solubilised, resulting in an increased absorbance reading.

In Figure 3 further evidence for the shift from unimer to micelle for the 30:60 MPC:DEA copolymer in response to increased pH can be seen. At pH4 (grey shaded curve) only unimers with a mean diameter of 11.3nm are present, however when the pH is raised to pH8 (black shaded curve) there is a clear increase in mean diameter from 11.3nm up to 37.5nm, indicating the unimers have undergone micellar self assembly in response to increased pH.

These initial studies indicate that MPC-DEA polymeric micelles systems have the potential to act as a carrier for hydrophobic drugs, with the drug being easily loaded by simple entrapment, and the amount of drug carried being tunable by pH and DEA block length.

CLAIMS

1. An aqueous composition comprising an amphiphilic block copolymer having a hydrophilic block and a hydrophobic block, dispersed in the solution, and a biologically active compound associated with the polymer, characterised in that the hydrophilic block has pendant zwitterionic groups.

2. A composition according to claim 1 in which the biologically active molecule is associated by hydrophobic interactions with the copolymer.

3. A composition according to claim 2 in which the biologically active compound has a measured and/or calculated partition coefficient between octane and water, log P or clog P of at least 1.0, preferably at least 1.5.

4. A composition according to any preceding claim in which the copolymer is dispersed in the form of micelles.

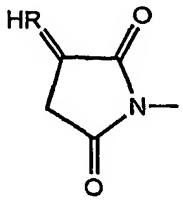
5. A composition according to any preceding claim wherein the hydrophilic block is formed by radical polymerisation of ethylenically unsaturated monomers.

6. A composition according to claim 5 in which the monomers comprise a zwitterionic monomer.

7. A composition according to claim 6 in which the zwitterionic monomer has the general formula

Y B X I

in which Y is an ethylenically unsaturated group selected from H_2C=CR-CO-A-, H_2C=CR-C_6H_4-A^1-, H_2C=CR-CH_2A^2, R^2O-CO-CR=CR-CO-O, RCH=CH-CO-O-, RCH=C($COOR^2$)CH_2-CO-O,



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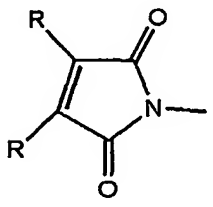


A is -O- or NR^1;

A^1 is selected from a bond, $(CH_2)_l A^2$ and $(CH_2)_l SO_3$- in which l is 1 to 12;

A^2 is selected from a bond, -O-, O-CO-, CO-O, CO-NR^1-, -NR^1-CO, O-CO-NR^1-, NR^1-CO-O-;

R is hydrogen or C_{1-4} alkyl;

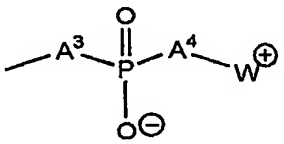
R^1 is hydrogen, C_{1-4} alkyl or BX;

R^2 is hydrogen or C_{1-4} alkyl;

B is a bond, or a straight branched alkanediyl, alkylene oxaalkylene, or alkylene (oligooxalkylene) group, optionally containing one or more fluorine substituents;

X is a zwitterionic group.

8. A composition according to claim 7 in which X is a group of the general formula II



II

in which the moieties A^3 and A^4, which are the same or different, are -O-, -S-, -NH- or a valence bond, preferably -O-, and W^+ is a group comprising an ammonium, phosphonium or sulphonium cationic group and a group linking the anionic and cationic moieties which is preferably a C_{1-12}-alkanediyl group,

preferably in which W^+ is a group of formula $-W^1-N^+R^3_3$, $-W^1-P^+R^4_3$, $-W^1-S^+R^4_2$ or $-W^1$-Het$^+$ in which:

W^1 is alkanediyl of 1 or more, preferably 2-6 carbon atoms optionally containing one or more ethylenically unsaturated double or triple bonds, disubstituted-aryl (arylene), alkylene arylene, arylene alkylene, or alkylene aryl alkylene, cycloalkanediyl, alkylene cycloalkyl, cycloalkyl alkylene or

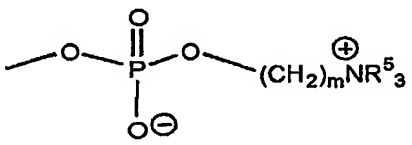
alkylene cycloalkyl alkylene, which group W^1 optionally contains one or more fluorine substituents and/or one or more functional groups; and

either the groups R^3 are the same or different and each is hydrogen or alkyl of 1 to 4 carbon atoms, preferably methyl, or aryl, such as phenyl, or two of the groups R^3 together with the nitrogen atom to which they are attached form an aliphatic heterocyclic ring containing from 5 to 7 atoms, or the three groups R^3 together with the nitrogen atom to which they are attached as heteroaromatic ring having 5 to 7 atoms, either of which rings may be fused with another saturated or unsaturated ring to form a fused ring structure containing from 5 to 7 atoms in each ring, and optionally one or more of the groups R^3 is substituted by a hydrophilic functional group, and

the groups R^4 are the same or different and each is R^3 or a group OR^3, where R^3 is as defined above; or

Het is an aromatic nitrogen-, phosphorus- or sulphur-, preferably nitrogen-, containing ring, for example pyridine.

9. A composition according to claim 7 in which X has the general formula III



III

where the groups R^5 are the same or different and each is hydrogen or C_{1-4} alkyl, and m is from 1 to 4, in which preferably the groups R^5 are the same preferably methyl.

10. A composition according to any of claims 7 to 9 in which Y is H_2C=CR-CO-A- in which R is H or methyl and -A- is -O- or -NH-.

11. A composition according to any of claims 7 to 10 in which B is a C_{2-6}-alkanediyl group.

12. A composition according to any of claims 7 to 11 in which the zwitterionic monomer is 2-methacryloyloxyethyl-2'-trimethylammonium ethyl phosphate inner salt.

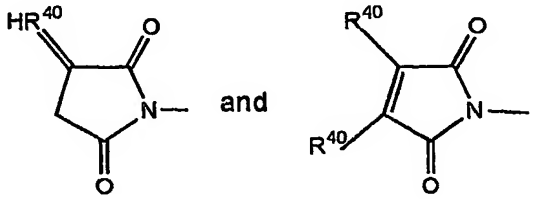
13. A composition according to any preceding claim in which the hydrophobic block comprises pendant groups which are ionisable, having a pK_A or pK_B in the range 4 to 10, preferably in the range 5 to 9, for instance in the range 6 to 8.

14. A composition according to claim 13 in which the hydrophobic block is formed by radical polymerisation of ethylenically unsaturated monomers.

15. A composition according to claim 14 in which the monomers from which the hydrophobic block is formed have the general formula

$$Y^1B^1Q$$

in which Y^1 is an ethylenically unsaturated group selected from $H_2C=CR^{40}$-CO-A^8-, $H_2C=CR^{40}$-C_6H_4-A^9-, $H_2C=CR^{40}$-CH_2A^{10}, $R^{42}O$-CO-$CR^{40}=CR^{40}$-CO-O, $R^{40}CH=CH$-CO-O-, $R^{40}CH=C(COOR^2)CH_2$-CO-O,



A^8 is -O- or NR^{41};

A^9 is selected from a bond, $(CH_2)_qA^{10}$ and $(CH_2)_q$ SO_3- in which q is 1 to 12;

A^{10} is selected from a bond, -O-, O-CO-, CO-O-, CO-NR^{41}-, -NR^{41}-CO, O-CO-NR^{41}-, NR^{41}-CO-O-;

R^{40} is hydrogen or C_{1-4} alkyl;

R^{41} is hydrogen, C_{1-4} alkyl or B^1Q;

R^{42} is hydrogen or C_{1-4} alkyl;

B^1 is a bond, or a straight branched alkanediyl, alkylene oxaalkylene, or alkylene (oligooxalkylene) group, optionally containing one or more fluorine substituents; and

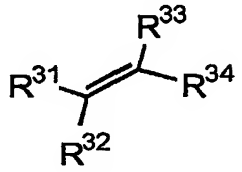
Q is a cationic or cationisable group of the formula -NR^{43}_p, -PR^{43}_p and SR^{43}_r, in which p is 2 or 3, r is 1 or 2, the groups R^{43} are the same or different

and each is selected from the group consisting of hydrogen, C_{1-24} alkyl and aryl, or two of the groups R^{43} together with the heteroatom to which they are attached from a 5 to 7 membered heterocyclic ring or three R^{43} groups together with the heteroatom to which they are attached form a 5 to 7 membered heteroaromatic ring, either of which rings may be fused to another 5 to 7 membered saturated or unsaturated ring, and any of the R^{43} groups may be substituted by amino or hydroxyl groups or halogen.

16. A composition according to claim 15 in which Q is NR^{43}_2 in which each R^{43} is H or C_{1-4}-alkyl.

17. A composition according to claim 5 or claim 14 in which the ethylenically unsaturated monomers include comonomer.

18. A composition according to claim 17 in which the or each comonomer has the general formula X



X

in which R^{31} is selected from hydrogen, halogen, C_{1-4} alkyl and groups $COOR^2$ in which R^2 is hydrogen and C_{1-4} alkyl;

R^{32} is selected from hydrogen, halogen and C_{1-4} alkyl;

R^{33} is selected from hydrogen, halogen, C_{1-4} alkyl and groups $COOR^2$ provided that R^{31} and R^{33} are not both $COOR^2$; and

R^{34} is a C_{1-10} alkyl, a C_{1-20} alkoxycarbonyl, a mono-or di-(C_{1-20} alkyl) amino carbonyl, a C_{6-20} aryl (including alkaryl) a C_{7-20} aralkyl, a C_{6-20} aryloxycarbonyl, a C_{1-20} -aralkyloxycarbonyl, a C_{6-20} arylamino carbonyl, a C_{7-20} aralkyl-amino, a hydroxyl or a C_{2-10} acyloxy group, any of which may have one or more substituents selected from halogen atoms, alkoxy, oligo-alkoxy, aryloxy, acyloxy, acylamino, amine (including mono and di-alkyl amino and trialkylammonium in which the alkyl groups may be substituted), carboxyl, sulphonyl, phosphoryl, phosphino, (including mono- and di- alkyl phosphine and tri-alkylphosphonium), zwitterionic, hydroxyl groups, vinyloxycarbonyl

and other vinylic or allylic substituents, and reactive silyl or silyloxy groups, such as trialkoxysilyl groups;

or R^{34} and R^{33} or R^{34} and R^{32} may together form -$CONR^{35}CO$ in which R^{35} is a C_{1-20} alkyl group.

19. A composition according to claim 18 in which the comonomer is a C_{1-24} alkyl(alk)-acrylate or -acrylamide, mono- or di- hydroxy-C_{1-6}-alkyl(alk)-acrylate, or acrylamide, oligo(C_{2-3} alkoxy) C_{2-18}-alkyl (alk)-acrylate, or -acrylamide, styrene, vinylacetate or N-vinyllactam.

20. A composition according to any preceding claim in which the polydispersity of molecular weight of each of the blocks is less than 2.0, preferably less than 1.5, more preferably in the range 1.1 to 1.4.

21. A composition according to any of claims 5 to 13 in which the degree of polymerisation of the hydrophilic block is in the range 2 to 1000, preferably 5 to 250, more preferably 10 to 100.

22. A composition according to any of claims 14 to 16 in which the degree of polymerisation of the hydrophobic block is in the range 5 to 2000, preferably 10 to 500, more preferably 20 to 250.

23. A composition according to claim 21 or 22 in which the ratio of the degrees of polymerisation of the hydrophobic to hydrophilic blocks is in the range 1:5 to 10:1, preferably 1:1 to 5:1.

24. A composition according to claim 5 or claim 14 in which at least one of the blocks and preferably both the blocks are formed by controlled radical polymerisation.

25. A composition according to claim 24 in which polymerisation is by atom or group transfer radical polymerisation.

26. A composition according to any preceding claim in which the biologically active molecule is a cytotoxic compound, preferably an anti-cancer drug.

27. A method of forming an aqueous composition comprising an amphiphilic block copolymer and a biologically active compound, in which the copolymer comprises a hydrophilic block and a hydrophobic block and

an aqueous dispersion of empty copolymer micelles is formed and the micellar dispersion is contacted with biologically active compound under conditions such that the biologically active compound becomes associated with the copolymer in the micelles, characterised in that the hydrophilic block has pendant zwitterionic groups.

28. A method according to claim 27 in which the biologically active compound has a partition coefficient between octane and water (log P) of at least 1.0, preferably at least 1.5, for instance 2.0 or higher.

29. A method according to claim 27 or claim 28 in which the hydrophobic block of the copolymer comprises ionisable groups, and in which the empty copolymer micelles are formed by a process comprising:

a) a first copolymer dissolution step in which the block copolymer, with the groups of hydrophobic block in at least partially ionised form, is dissolved in an aqueous liquid, and

b) a second micelle forming step in which the conditions in the solution are adjusted so that the ionised groups are converted at least partially to their ionisable form, whereby the copolymer is above the critical micelle concentration in the aqueous liquid and micelles are formed.

30. A method according to claim 29 in which the conditions which are adjusted are of temperature and/or pH.

31. A method according to claim 29 or 30 in which the ionisable groups are primary, secondary or tertiary amine groups and in which the micelle forming step involves raising the pH whereby the ionised groups become deprotonated.

32. A method according to any of claims 27 to 31 in which the biologically active compound is in solid form when it is contacted with the aqueous dispersion of empty micelles.

33. A method according to any of claims 27 to 32 in which the biologically active compound is in solution in an organic solvent when it is contacted with the aqueous dispersion of empty micelles.

34. A method according to claim 27 having the further features of any of claims 2 to 26.

ABSTRACT

DRUG CARRIERS

An aqueous composition comprises an amphiphilic block copolymer, having a hydrophilic block comprising pendant zwitterionic groups and a hydrophobic block, and a biologically active compound associated with the polymer. The polymer is preferably in the form of micelles, and preferably the biological active is a hydrophobic drug, for instance having a calculated or experimentally determined logP of at least 1.0, where P is the octane:water partition coefficient. The hydrophilic block is preferably formed from acrylic monomer including phosphorylcholine groups. The hydrophobic group is suitably formed from monomer which has groups which can be ionised at useful pH's, especially tertiary amine groups. Micelles may be formed by dissolving the block copolymer in aqueous solvent at a pH at which the amine groups are protonated then raising the pH to a value at which the amine groups are substantially deprotonated, whereupon micelles spontaneously form. The preformed micelles are then contacted with active, under conditions such that solubilisation of the active occurs. The active may be a water-insoluble drug, for instance for tumour treatment.

Figure 1. Percentage Solubilization of Orange OT

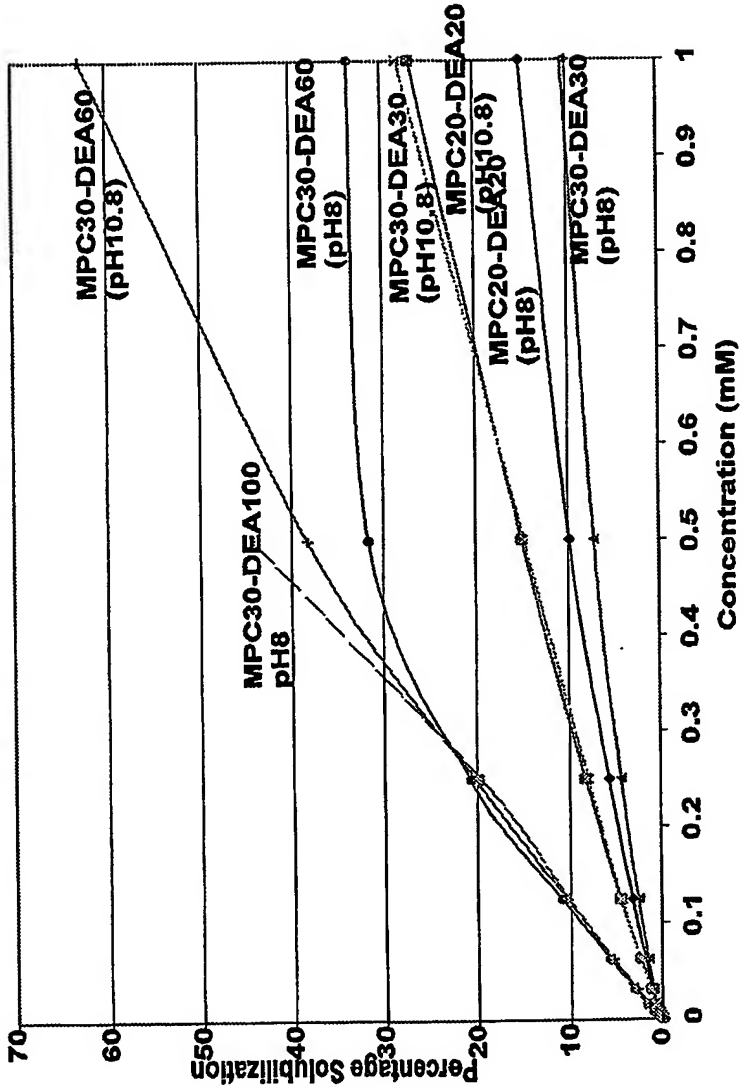


Figure 2 MPC30-DEA60 Orange OT Solubilization

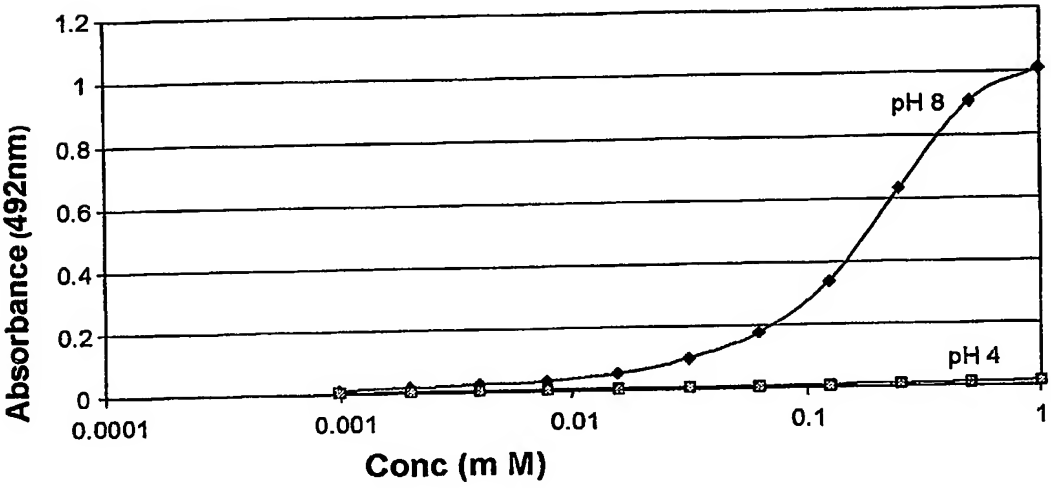
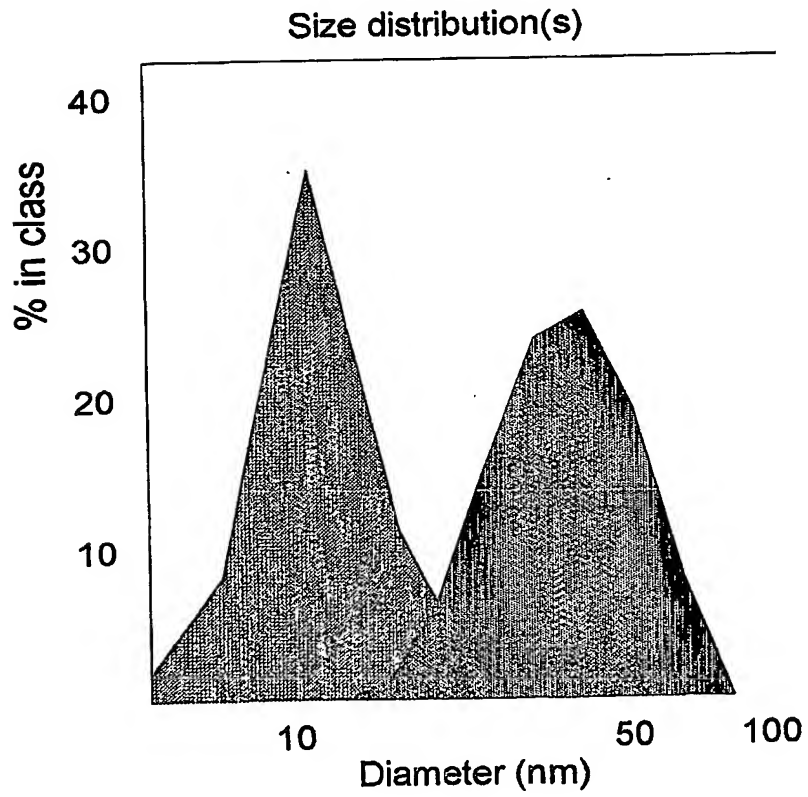


Figure 3. Particle size (nm)



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